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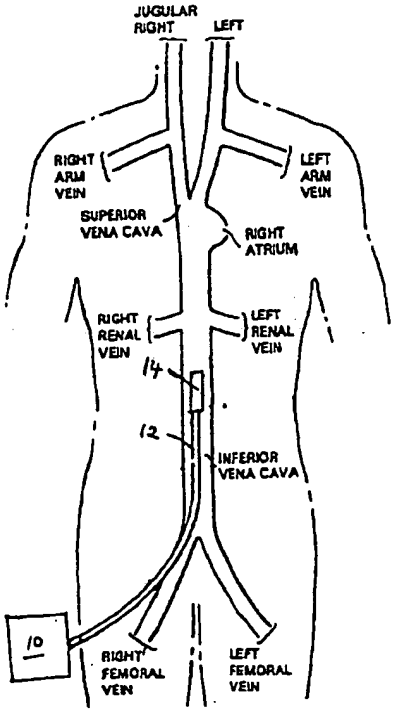

(57) Abstract: The use of an intravascular cooling element to induce hypothermia in connection with a medical procedure. According to a first aspect of the present invention, a coronary bypass procedure is conducted in which a patient's blood is oxygenated with the patient's lungs and in which blood is circulated using the patient's heart or using an intracorporeal pump. The procedure preferably comprises: (a) positioning a heat transfer element in a blood vessel of a patient; (b) cooling the body of the patient to less than 35°C, more preferably 32±2°C, using the heat transfer element; and (c) forming a fluid communicating graft between an arterial blood supply and the coronary artery. The body of the patient is preferably heated to about 37°C using the heat transfer element subsequent to the step of forming the fluid communicating graft. According to a further aspect of the invention, a hypothermic medical procedure is provided while a patient is in a conscious or semiconscious state, comprising (a) administering a beta-blocking drug to the patient; b) delivering a heat transfer element to a blood vessel of the patient; and c) cooling a region of the patient or the body of the patient to less than 35°C using the heat transfer element. According to yet a further aspect of the invention, a method is provided which comprises: (a) inducing hypothermia in a human patient in need of neural protection due to ischemic neural conditions, the step of inducing hypothermia comprising (i) positioning a heat transfer element in a blood vessel of a patient and (ii) cooling the body of the patient or a region of the body of the patient to less than 35°C using the heat transfer element; and (b) administering to the patient a therapeutic agent selected from (i) a free-radical scavenger, (ii) an N-methyl-D-aspartame receptor antagonist and (iii) an antipyretic agent, the therapeutic agent being provided in an amount effective to supplement neural protection provided by the step of inducing hypothermia.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

MEDICAL PROCEDURE

This application is a continuation-in-part of serial number 09/539,932 filed 3/31/00, which is a continuation-in-part of serial number 09/306,866 filed 5/7/99 and serial number 09/373,112, filed 8/11/99, the latter being a continuation-in-part of serial number 09/292,532 filed 4/15/99, which is a continuation-in-part of serial number 09/103,342 filed 6/23/98 and serial number 09/052,545 filed 3/31/98 and serial number 09/047,012 filed 3/24/98, the last of which is a continuation-in-part of serial number 09/012,287, filed 1/23/98, now U.S. Patent Number 6,051,019 issued April 18, 2000. Each of these disclosures is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to the use of an intravascular cooling element to induce hypothermia in connection with medical procedures.

BACKGROUND OF THE INVENTION

A number of approaches have been developed for treating coronary artery disease. In less severe cases, it is often sufficient to merely treat the symptoms with pharmaceuticals or to treat the underlying causes of the disease with lifestyle modification. In more severe cases, the coronary blockage can be treated endovascularly or percutaneously using techniques such as balloon angioplasty, atherectomy, laser ablation, stents, and the like.

In cases where these approaches have failed or are likely to fail, it is often necessary to perform a coronary artery bypass graft procedure ("coronary bypass procedure"). In this procedure, direct access to the heart is first achieved. This is

usually done by opening the chest by median sternotomy and spreading the left and right rib cage apart. The pericardial sac is then opened to achieve direct access to the heart. Next, a blood vessel or vessels for use in the graft procedure are mobilized from the patient. This usually entails mobilizing either a mammary artery or a saphenous vein, although other graft vessels may also be used.

A heart-lung or cardiopulmonary bypass is then performed. This procedure usually entails arterial and venous cannulation, connecting the bloodstream to a cardiopulmonary bypass system, cooling the body to about 32 degrees Celsius, cross clamping the aorta, and cardioplegic perfusion of the coronary arteries to arrest and cool the heart to about 4 degrees Celsius.

The arrest or stoppage of the heart is generally carried out because the constant pumping motion of the beating heart makes surgery upon the heart difficult. Cooling the body protects the organs from ischemia (a condition in which a tissue or organ does not receive a sufficient supply of blood), reduces the cardiac output requirement, and increases the systemic vascular resistance, which helps maintain perfusion and reduces the cardiopulmonary circuit primary volume.

Once cardiac arrest is achieved, a graft (or grafts) is attached to the relevant portions of a coronary artery (or arteries) followed by weaning from the cardiopulmonary bypass, restarting the heart, and decannulation. Finally the chest is closed.

After arresting the heart, the heart muscle, or myocardium, is protected and supported so that it does not suffer cellular or nerve damage that would prevent the heart from working properly when it is started again. There are two important aspects to the process of myocardial protection: (1) reducing the oxygen demand of the heart muscle; and (2) adequately oxygenating the heart muscle and maintaining the proper chemical balance so that cellular damage does not occur. One common technique for doing so is known as cold cardioplegia.

During this procedure, the coronary arteries must be isolated to prevent reperfusion of the myocardium with warm oxygenated blood from the cardiopulmonary bypass system that would wash out the cardioplegic agent and prematurely start the heart beating again. The most common way to isolate the

coronary arteries is by aortic cross clamping, which is normally implemented in the following fashion. Before stopping the heart, the patient is prepared by placement of an arterial cannula and a venous cannula, which are connected to the cardiopulmonary bypass system. The cardiopulmonary bypass system takes over the functions of the heart and the lungs of the patient by pumping and oxygenating the blood while the heart is stopped. Once the cardiopulmonary bypass system is connected and started, the ascending aorta can be cross-clamped to isolate the coronary arteries from the rest of the systemic arterial circulation. Then, cardioplegic arrest is induced by injecting 500-1000 cc of cardioplegic solution into the aortic root using a needle or cannula which pierces the wall of the ascending aorta upstream of the cross clamp.

Unfortunately, significant complications may result from such procedures. For example, application of an external cross-clamp to a calcified or atheromatous aorta may cause the release of emboli into the brachiocephalic, carotid or subclavian arteries with serious consequences such as strokes.

Systems have been proposed in which the aorta is occluded without cross clamping. For example, U.S. Patent No. 5,957,879 describes systems that include an aortic occlusion device having a balloon to occlude the ascending aorta and a lumen to deliver cardioplegic fluid for arresting the patient's heart. The aortic occlusion device replaces the conventional external cross-clamp and is said to reduce the amount of displacement and distortion of the aorta. Nonetheless, distortion is not eliminated, and the risk of emboli release remains present.

Other complications can arise from the cardiopulmonary bypass system, which includes mechanical blood pumps, an oxygenator, a heat exchanger, blood reservoirs and filters, and several feet of tubing to transport the blood from the patient on the operating table to the heart-lung machine located nearby and back to the patient. Such systems can cause complications due to the exposure of blood to foreign surfaces, which result in the activation of virtually all the humoral and cellular components of the inflammatory response, as well as some of the slower reacting specific immune responses. Other complications from cardiopulmonary bypass include loss of red blood cells and platelets due to shear stress damage. In

addition, cardiopulmonary bypass requires the use of an anticoagulant, such as heparin. This may, in turn, increase the risk of hemorrhage. Finally cardiopulmonary bypass sometimes necessitates giving additional blood to the patient. The additional blood, if from a source other than the patient, may expose the patient to blood-borne diseases.

Due to the risks noted above, others have attempted to perform a coronary artery bypass graft procedure without occluding the aorta and without cardiopulmonary bypass.

For example, attempts have been made wherein surgery is performed on a beating heart. The technique of operating on the beating heart, however, is difficult, due to the rapid movement of the heart, and can at present only be applied to single vessel bypassing procedures. Moreover, partial aortic cross clamping is generally implemented, which can dislodge emboli.

In other reported procedures, surgeons have been experimenting with a technique that involves stopping or nearly stopping the heart and supporting circulation with a small pump positioned in the patient's vasculature (i.e., an intracorporeal pump). See, for example, M. S. Sweeney, "The Hemopump in 1997: A Clinical, Political, and Marketing Evolution", *Ann. Thorac. Surg.*, 1999, Vol. 68, pp. 761-3 in which a coronary bypass procedure is described that uses a Medtronic Hemopump® for circulatory support and the patient's own lungs from oxygenation. Esmolol, a short acting beta-blocker, was administered to make the heart more tranquil during surgery. The interior surface area of the Hemopump is greatly reduced relative to traditional cardiopulmonary bypass systems, reducing the complications of such surfaces.

Unfortunately, it can be difficult to provide adequate circulation with a pump of this type, increasing the risk of ischemia. Moreover, while many of the dangers associated with cardiopulmonary bypass systems are avoided, certain benefits of such a system are also lost. For example, hypothermia is no longer induced in the patient, which serves to lower oxygen demand and which induces vasoconstriction, supporting perfusion. Each of these effects serves to protect the organs from ischemic damage.

Still other techniques have been proposed in which the heart is stopped or nearly stopped (e.g., placed in a reversible, temporary heart block) by locally delivering drugs, such as beta-blockers. At the same time, the heart is continuously paced by external pacemaker stimulation. In this way, alternating periods of heartbeat and heart arrest (e.g., up to 15 seconds) can be established, providing the surgeon with short intervals in which he or she can work on a stilled heart without resorting to a pump for supporting circulation. One such system is the TRANSARREST system of Corvascular, Inc., Palo Alto, CA. Still other methods are known in which surgery is facilitated by stopping or slowing the heart though electrical stimulation of the vagus nerve. See, e.g., U.S. Patent Nos. 5,913,876 and 6,006,134.

Unfortunately, as in the above case wherein the Hemopump supports circulation, these techniques result in less than ideal circulation and do not provide a hypothermic effect, increasing the risk of ischemia.

Medical procedures are also known in which hypothermia is induced in a conscious or semiconscious person, for example, where hypothermia is induced in a stroke victim to reduce ischemic damage. However, in such patients, hypothermia activates the sympathetic nervous system, resulting in a significant norepinephrine response. Norepinephrine, in turn, binds to beta-receptor sites, including those in the heart, causing the heart to beat harder and more rapidly, frequently resulting in cardiac arrythmia and increasing the risk of myocardial ischemia. Norepinephrine also causes peripheral vasoconstriction, frustrating relief of patient discomfort, for example, by using heating blankets.

Medical procedures are also known in which hypothermia is used to reduce brain injury caused by a variety of neurological insults such as global ischemia, focal ischemia or traumatic brain injury. *See, e.g.,* WO 99/48449.

Evidence of a neuroprotective effect has also been reported in rats upon post-ischemic treatment with hypothermia and an antipyritic/anti-inflammatory drug, dipyrone (Coimbra et al., "Long-lasting Neuroprotective Effect of Postischemic Hypothermia and Treatment With an Anti-Inflammatory/Antipyretic Drug", *Stroke* 27(9), pp. 1578-1585 (1996)) and upon pre- and post-ischemic

treatment with a free-radical scavenger and lipid peroxidation inhibitor, tirilazad mesylate, and a calcium antagonist and a noncompetitive antagonist of N-methyl-D-aspartame, magnesium (Schmid-Elsaesser et al., "Combination Drug Therapy and Mild Hypothermia" *Stroke* 30(9), pp. 1891-1899 (1999). Whole body hypothermia was induced in the rats by use of ice packs or by spraying alcohol onto the chest and abdominal skin, which was placed in contact with a metallic surface.

SUMMARY OF THE INVENTION

The present invention is directed to improvements in the prior art. According to a first aspect of the present invention, a coronary bypass procedure is conducted in which the patient's blood is oxygenated with the patient's lungs and in which blood is circulated using the patient's heart or using an intracorporeal pump. The procedure preferably comprises: (a) positioning a heat transfer element in a blood vessel of a patient; (b) cooling the body of the patient to less than 35°C, more preferably 32±2° C, using the heat transfer element; and (c) forming a fluid communicating graft between an arterial blood supply and the coronary artery.

The body of the patient is desirably heated to about 37 °C using the heat transfer element subsequent to the step of forming the fluid communicating graft.

Numerous variations are possible. For example, the step of forming a fluid communicating graft between the arterial blood supply and the coronary artery can be performed on a beating heart during bradycardia of the heart that occurs upon cooling the patient's body.

In another embodiment, the heart can be arrested or nearly arrested during at least a portion of the step of forming the fluid communicating graft. For example, the heart can be chemically arrested (e.g., using one or more beta-blockers), or the heart can be electrically arrested. While heart is arrested, the patient's circulation is preferably supported with a pump positioned in the patient's vasculature. In a preferred embodiment, the pump is at least partially positioned in the left ventricle and is introduced into the patient through the femoral artery.

In yet another embodiment, the heartbeat is intermittently arrested and stimulated, and at least a portion of the step of forming the fluid communicating

graft is carried out during periods of heartbeat arrest. For example, the heart can be chemically arrested (e.g., with one or more beta blockers) and electrically stimulated. Alternatively, the heart can be both electrically arrested and electrically stimulated. In this way, the use of a pump can be avoided.

The heat transfer element can be positioned, for example, in the venous vasculature, where it is preferably introduced via the femoral vein. More preferably, the heat transfer element is positioned in the inferior vena cava via the femoral vein. In this instance, the heat transfer element is preferably about 4 to 5 mm in diameter.

In one preferred embodiment, the heat transfer element is attached to the distal end of a flexible catheter, and the catheter is used in the step of positioning the heat transfer element in the blood vessel. The catheter is also used to convey chilled or heated fluid to the interior of the heat transfer element.

The catheter is desirably configured for efficient heat transfer. As an example, it is preferred that the heat transfer element absorbs at least 150 Watts of heat during cooling. To promote efficient heat transfer, the heat transfer element can comprise a plurality of exterior and interior surface irregularities, wherein the exterior and interior surface irregularities are preferably shaped and arranged to create mixing in the blood and in the fluid within the heat transfer element, respectively. In a preferred embodiment, the interior and exterior surface irregularities comprise one or more helical ridges and one or more helical grooves.

According to a second aspect of the invention, a hypothermic medical procedure is provided comprising (a) administering a beta-blocking drug to a patient; (b) delivering a heat transfer element to a blood vessel of a patient; and (c) cooling a region of the patient or the body of the patient to less than 35°C using the heat transfer element while the patient is in a conscious or semiconscious state. Preferably, the beta-blocking drug is administered after delivering the heat transfer element to the blood vessel. Preferred beta-blocking drugs for this aspect of the invention include ∃1 blockers, ∃1∃2 blockers, and ∀∃1∃2 blockers. Preferred ∃1 blockers include acebutolol, atenolol, betaxolol, bisoprolol, esmolol and metoprolol. Preferred ∃1∃2 blockers include carteolol, nadolol, penbutolol,

pindolol, propranolol, sotalol and timolol. Preferred ∀∃1∃2 blockers include carvedilol and labetalol.

According to a third aspect of the invention, a method is provided which comprises: (a) inducing hypothermia in a human patient in need of neural protection due to ischemic neural conditions, the step of inducing hypothermia comprising (i) positioning a heat transfer element in a blood vessel of a patient and (ii) cooling the body of the patient or a region of the body of the patient to less than 35°C using the heat transfer element; and (b) administering to the patient a therapeutic agent selected from (i) a free-radical scavenger, (ii) an N-methyl-D-aspartame receptor antagonist and (iii) an antipyretic agent, the therapeutic agent being provided in an amount effective to supplement neural protection provided by the step of inducing hypothermia.

The body of the patient or the region of the body of the patient is preferably cooled to 30 to 35 °C. The heat transfer element can be placed in either the venous or arterial vasculature. When the brain is to be cooled, the heat transfer element is preferably positioned in the common carotid artery, the internal carotid artery, or concurrently in both the common carotid artery and the internal carotid artery.

In some preferred embodiments, the therapeutic agent is an antipyretic agent that has anti-inflammatory properties as well as antipyretic properties, more preferably dipyrone. In others, the therapeutic agent is a free radical scavenger, more preferably tirilazad or a salt thereof. In still other preferred embodiments, the therapeutic agent is the N-methyl-D-aspartame receptor antagonist, more preferably dextromethorphan or a salt thereof. In yet other preferred embodiments, both the free radical scavenger and the N-methyl-D-aspartame receptor antagonist are administered to the patient.

In some embodiments, the hypothermia is induced and the therapeutic agent is administered after the patient has experienced the ischemic neural conditions, such as in those cases where the patient has experienced cerebral ischemia, a stroke, or ischemia of the spinal cord. Under these circumstances, the hypothermia is preferably induced within 6 to 12 hours after the patient has experienced the ischemic neural conditions.

In other embodiments, the hypothermia is induced and the therapeutic agent is administered before the patient experiences the ischemic neural conditions, such as in those cases where the ischemic neural conditions arise in connection with brain surgery.

Advantages of the present invention include the elimination of aortic occlusion and cardiopulmonary bypass systems during coronary bypass surgery.

Where beating heart procedures are incorporated, another advantage of the present invention is the promotion of a bradycardia of the heart, simplifying surgery.

Another advantage of the present invention include a reduction in the risk of ischemia associated with techniques that provide circulatory flow rates that are significantly lower than ordinary cardiac output and with techniques incorporating vasodilatory substances.

Yet another advantage of the present invention is that the risk of cardiac arrythmia and myocardial ischemia is reduced in connection with medical procedures that induce hypothermia in conscious or semiconscious patents.

Yet another advantage of the present invention is that hypothermic neural protection in a human patient can be enhanced by administering a therapeutic agent to the patient in combination with the hypothermia.

The above and other embodiments and advantages of the invention will become apparent to those of ordinary skill in the art upon reading the description and claims to follow.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic representation of the use of a heat transfer element to cool the body, according to an embodiment of the invention.

Figure 2 is an elevation view of a mixing inducing heat transfer element within a blood vessel in accordance with an embodiment of the invention.

Figure 3 is an elevation view of a heat transfer element used in accordance with an embodiment of the invention.

Figure 4 is a longitudinal section view of the heat transfer element of Figure 3.

Figure 5 is a schematic representation of the use of a heat transfer element to cool the brain of a patient, according to an embodiment of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention now will be described more fully hereinafter. This invention may, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein.

According to one aspect of the present invention, a procedure is provided by which a surgeon is able to perform a coronary bypass procedure with hypothermic protection, while at the same time avoiding many of the disadvantages associated with the use of traditional external cardiopulmonary bypass systems and aortic clamping procedures.

In one embodiment of the present invention, a heat transfer element is provided within a blood vessel of the body such that blood is cooled *in vivo* upon contact with the heat transfer element.

The heat transfer element can be provided in either arterial or venous blood vessels. One preferred location for the heat transfer element is the inferior vena cava, which typically ranges from 15 mm to 25 mm in diameter. A preferred method by which the heat transfer element is provided at this position is via entry at the femoral vein.

Figure 1 is a schematic representation of the use of a heat transfer element in cooling the body of a patient. The apparatus shown in Figure 1 includes a working fluid supply 10, preferably supplying a chilled aqueous solution, a supply catheter 12 and a heat transfer element 14. The supply catheter 12 may have a substantially coaxial construction. An inner coaxial lumen within the supply catheter 12 receives coolant from the working fluid supply 10. The coolant travels the length of the supply catheter 12 to the heat transfer element 14 that serves as the cooling tip of the catheter. At the distal end of the heat transfer element 14, the coolant exits an insulated interior lumen and traverses the length of the heat transfer element 14 in

order to decrease the temperature of the surface of the heat transfer element 14. The coolant then traverses an outer lumen of the supply catheter 12 so that it may be disposed of or recirculated. The supply catheter 12 is a flexible catheter having a diameter sufficiently small to allow its distal end to be inserted percutaneously into an accessible blood vessel, shown in Figure 1 as the right femoral vein. The supply catheter 12 is sufficiently long to allow the heat transfer element 14 at the distal end of the supply catheter 12 to be passed through the vascular system of the patient and placed in the blood vessel of interest, here the inferior vena cava. The method of inserting the catheter into the patient and routing the heat transfer element 14 into a selected artery or vein is well known in the art.

In the embodiment of Figure 1, the narrowest blood vessel encountered by the heat transfer element as it travels to the inferior vena cava is the femoral artery, which generally ranges from 5 to 8 mm in diameter. Accordingly, in this embodiment of the invention, the diameter of the heat transfer element is about 4 to 5 mm in diameter.

In order to obtain the benefits associated with hypothermia during a coronary bypass procedure, it is desirable to reduce the temperature of the blood flowing within the body to less than 35°C, more preferably between 30 and 35°C, and most preferably 32±2°C. Given a typical blood flow rate of approximately 2.5 to 4 l/min, more typically about 3.5 l/min, in the inferior vena cava, the heat transfer element preferably absorbs 200 to 300 Watts of heat when placed in this vein, in order to induce the desired cooling effect. Approximate cooling time is 15 to 30 minutes.

Cooling the body to less than 35°C provides a number of desirable effects. First, cooling will induce a bradycardia of the heart. Reduced heart rates corresponding to about 2/3 of the normal heart rate are common at the preferred temperature of 32±2° C. By slowing the beating of the heart, the present invention facilitates surgery during beating heart procedures. Such procedures are well known in the art. For example, the performance of coronary surgery on the beating heart is described by Benetti et al in "Coronary Revascularization With Arterial Conduits Via a Small Thoracotomy and Assisted by Thoracoscopy, Although

Without Cardiopulmonary Bypass", Cor. Europatum, 4(1): 22-24 (1995), and by Westaby, "Coronary Surgery Without Cardiopulmonary Bypass" in the March, 1995 issue of the British Heart Journal. Additional discussion of this subject matter can be found in Benetti et al, "Direct myocardial revascularization without extracorporeal circulation. Experience in 700 patients", Chest, 100(2): 312-16 (1991), Pfister et al, "Coronary artery bypass without cardiopulmonary bypass" Ann. Thorac. Surg., 54:1085-92 (1992), and Fanning et al, "Reoperative coronary artery bypass grafting without cardiopulmonary bypass", Ann. Thorac. Surg., 55:486-89 (1993). Each of the above articles is hereby incorporated by reference.

Moreover, the general anesthesia associated with coronary bypass techniques is often accompanied by vasodilation in the patient, which decreases organ perfusion and hence increases the risk of ischemia. This effect, however, is combated by the hypothermia induced in accordance with the present invention, which promotes vasoconstriction.

Cooling the body also protects the organs from ischemic damage due to low circulatory flow rates or due to emboli formation. For example, as previously noted, procedures are known in the art in which (1) the heart is intermittently stopped and restarted or (2) the heart is stopped and a small intracorporeal pump is used to provide circulatory support. These techniques and others like them allow the surgeon to operate on a still or nearly still heart. However, each of these techniques also places the patient at risk from ischemia. By lowering the body temperature of the patient to a preferred temperature of 32±2° C in accordance with the present invention, however, the oxygen demand of the bodily tissue, and hence the danger of ischemia associated with these procedures, is reduced.

More specifically, with some techniques in which alternating periods of heartbeat and heart arrest are provided, the heart is stopped or nearly stopped using drugs such as beta-blockers, and a pacing device is used to cause the heart to beat on demand. An example of one such system is the TRANSARREST system; Corvascular, Inc., Palo Alto, CA. In other techniques, the heart is momentarily stopped or slowed by electrically stimulating the vagus nerve. See, e.g., U.S. Patent Nos. 5,913,876 and 6,006,134, the disclosures of which are hereby incorporated by

reference. (As noted in U.S. Patent No. 5,913,876, one or more heart pacing devices, such as a Pace port-Swann pulmonary artery catheter, may be inserted in conventional fashion to the patient's heart and used to restore the beating of the heart during the surgery, in the event the heart is slow to revive after a nerve stimulating signal is turned off.) Each of these techniques is associated with a circulatory flow rate that can be significantly lower than normal cardiac output.

The risks of ischemia due to low circulatory flow rates, however, are reduced in accordance with an embodiment of the invention. In particular, before manipulating the heartbeat of the patient, a heat transfer element is inserted into the vasculature of the patient and the body temperature of the patient is reduced, preferably to 32±2° C. As noted above, by lowering the body temperature, the body's oxygen demand is reduced, decreasing the risk of ischemia. Moreover, a reduction in body temperature in accordance with the present invention is accompanied by vasoconstriction, which decreases the circulatory flow rate that is required for adequate organ perfusion and consequently further decreases the risk of ischemia.

The present invention is also useful in connection with techniques in which the heart is stopped or nearly stopped and an intracorporeal pump is used to support circulation. For example, techniques are known in which circulatory support is provided during coronary bypass by a pump positioned in the patient's aortic valve. See, for example, M. S. Sweeney, "The Hemopump in 1997: A Clinical, Political, and Marketing Evolution", *Ann. Thorac. Surg.*, 1999, Vol. 68, pp. 761-3, the entire disclosure of which is hereby incorporated by reference. In this reference, a coronary bypass operation is described in which esmolol, a short acting beta-blocker, is administered to calm the heart during surgery. A Medtronic Hemopump® is used for circulatory support and the patient's own lungs are used for oxygenation. At the core of the Hemopump is a small, rapidly turning Archimedes screw. The pump assembly is made of stainless steel and is attached to a silicone rubber inlet cannula. The cannula is positioned across the aortic valve and into the left ventricle. The pump assembly is catheter mounted to facilitate placement of the pump in its operating position. For example, the pump assembly

is ordinarily inserted into the femoral artery of the thigh, whereupon it is guided to the left ventricle. Once in place, the cannula acts to entrain blood and feeds it to the pump portion, which then pumps the blood into circulation via the aorta. The pump is operated by the creation of pulsing electromagnetic fields, which cause rotation of a permanent magnet, resulting in operation of the Archimedes screw. Electrical power is provided from a console outside the patient. The pumping action is axial and continuous (i.e., non-pulsatile). Due to the design of the Hemopump, rotational speeds on the order of 10,000 to 20,000 rpm can be used to produce blood flow of about four liters per minute or less (depending on the model) without significant hemolysis. Additional details are found in M.C. Sweeney and O.H. Frazier, "Device-supported myocardial revascularization; safe help for sick hearts", *Ann. Thorac. Surg.* 1992, 54: 1065-70 and U.S. Patent No. 4,625,712, the entire disclosures of which are hereby incorporated by reference.

This technique and others like it, however, are frequently associated with circulatory flow rates (i.e., about 4 l/min or less) that are lower than normal cardiac output (i.e., about 5 l/min for many people) placing the patient at ischemic risk. By lowering the body temperature of the patient to a preferred range of 32±2° C in accordance with the present invention, however, the blood vessels are constricted and oxygen demand of the bodily tissue is reduced, increasing organ perfusion and reducing the danger of ischemia for a given circulatory output.

As noted above, in a preferred embodiment of this first aspect of the invention, the heat transfer element is provided in the inferior vena cava, which is accessed via the femoral vein. In contrast, the Hemopump is preferably provided in the left ventricle, which is accessed via the femoral artery. In this way, both the heating element and the Hemopump can be concurrently placed in the body in a minimally invasive fashion.

According to another aspect of the invention, a hypothermic medical procedure is performed on a patient in a conscious or semiconscious state. An example of a situation where such a hypothermic medical procedure may be performed is one in which a patient has suffered a stroke and hypothermia is induced in the brain to reduce ischemic damage.

Such procedures can be performed either to cool the entire body of the patient or a region within the patient's body, typically an organ.

The entire body can be cooled using the procedures discussed above. For example, the heat transfer element is preferably provided in a venous blood vessel, more preferably the inferior vena cava, to effect cooling of the entire body.

In order to intravascularly regulate the temperature of a selected region, the heat transfer element may be placed in a feeding artery of the region to absorb or deliver the heat from or to the blood flowing into the region. The heat transfer element should be small enough to fit within the feeding artery while still allowing a sufficient blood flow to reach the region in order to avoid ischemic damage. By placing the heat transfer element within the feeding artery of a region, the temperature of the region can be controlled, while having less effect on the remaining parts of the body. Using the brain as an example, the common carotid artery supplies blood to the head and brain. The internal carotid artery branches off of the common carotid to directly supply blood to the brain. To selectively cool the brain, the heat transfer element is placed into the common carotid artery, or both the common carotid artery and the internal carotid artery. The internal diameter of the common carotid artery ranges from 6 to 8 mm and the length ranges from 80 to 120 mm. Thus, the heat transfer element residing in one of these arteries cannot be much larger than 4 mm in diameter in order to avoid occluding the vessel, which would result, for example, in ischemic damage.

When hypothermia is induced in a patient, less than desirable side effects can occur in the patient. For example, hypothermia is known to activate the sympathetic nervous system in a conscious or semiconscious patient, resulting in a significant norepinephrine response. Norepinephrine, in turn, binds to beta sites including those in the heart, causing the heart to beat harder and more rapidly, frequently resulting in cardiac arrythmia and increased risk of myocardial ischemia. In accordance with an embodiment of the present invention, however, a beta-blocker is administered to the patient. Without wishing to be bound by theory, it is believed that the beta-blocker offsets the norepinephrine binding noted above. In

general, the beta-blocker may be administered before the patient cooling commences, and preferably immediately before patient cooling commences.

Preferred beta-blockers for this aspect of the invention include ∃1 blockers, ∃1∃2 blockers and ∀∃1∃2 blockers. Preferred ∃1 blockers include acebutolol, atenolol, betaxolol, bisoprolol, esmolol and metoprolol. Preferred ∃1∃2 blockers include carteolol, nadolol, penbutolol, pindolol, propranolol, sotalol and timolol. Preferred ∀∃1∃2 blockers include carvedilol and labetalol.

The heightened demand that hypothermia places on the heart of conscious or semiconscious patents may also be relieved, for example, with heating blankets. However, vasoconstriction limits the heating ability of the heating blankets. Without wishing to be bound by theory, it is believed that the above-noted production of norepinephrine activates alpha-receptors, for example, in the peripheral blood vessels, causing this vasoconstriction. The vasoconstriction can be offset, in accordance with the present invention, by treating the patient with alpha-blockers when indicated, preferably before cooling is initiated. Preferred alpha-blockers include labetalol and carvedilol.

According to another aspect of the present invention, a procedure is provided in which hypothermia is induced in a human patient in need of neural protection due to ischemic neural conditions by positioning a heat transfer element in a blood vessel of the patient. To enhance the neural protection provided by the induced hypothermia, an effective amount of one or more therapeutic agents is administered to the patient, which therapeutic agents may include (a) an antipyretic agent, (b) a free-radical scavenger, and/or (c) an N-methyl-D-aspartame receptor antagonist.

Preferred antipyretic agents for the purposes of the present invention are antipyretic agents having anti-inflammatory properties as well as antipyretic properties, such as dipyrone. Dipyrone has been withdrawn or removed for the market in the U.S., but it is available from Hoechst AG. Determining the dosage forms, dosage amounts and dosage frequencies that are effective to supplement the neural protection provided by hypothermia is well within the abilities of those of

ordinary skill in the art. In the event that the ischemic neural conditions are associated with fever, such as that commonly associated with stroke, the antipyretic agent is administered until the risk of fever subsides, typically at least three days after hypothermia is suspended.

Preferred free radical scavengers for the purposes of the present invention include tirilazad or any pharmaceutically active salts thereof. Tirilazad mesylate, which is both a free-radical scavenger and a lipid peroxidation inhibitor, is manufactured by Upjohn under the trade name FREEDOX and is indicated to improve survival and functional outcome in male patients with aneurismal subarachnoid hemorrhage. Determining those dosage forms, dosage amounts and dosage frequencies that are effective to supplement the neural protection provided by hypothermia is well within the abilities of those of ordinary skill in the art.

Preferred N-methyl-D-aspartame receptor antagonists for the practice of the present invention include dextromethorphan, $MgCl_2$ and memantine, more preferably dextromethorphan and pharmaceutically active salts of the same. Dextromethorphan is commonly found in syrup form and is available from a variety of sources. A preferred dosage for dextromethorphan is 10 to 30 mg orally every four to eight hours for at least three days. Determination of other appropriate dosage forms, dosage amounts and dosage frequencies that are effective to supplement the neural protection provided by hypothermia is well within the abilities of those of ordinary skill in the art.

Combinations of the above therapeutic agents are also possible. For example, in one preferred embodiment, a free radical scavenger and an N-methyl-D-aspartame receptor antagonist are co-administered along with the hypothermia.

The method of the present invention is appropriate for various types of ischemic neural conditions, including ischemia of the spinal cord, cerebral ischemia including stroke, and so forth.

The need for neural protection due to ischemic neural conditions can occur in various contexts. In some instances, a patient has experienced an unanticipated ischemic injury, for example, due to physical trauma, such as that associated with an automobile accident, or due to a pathological event, such as a stroke. Under

such circumstances, it is preferred that hypothermia be induced and therapeutic agent be applied within 6 to 12 hours after the patient has experienced the ischemic injury.

In other instances, the patient is at risk of ischemic neural conditions due to a medical procedure such as cardiac surgery, brain surgery including anneurism surgery, and so forth. In these instances, it is preferred that hypothermia be induced and that the therapeutic agent be administered before to the medical procedure commences.

As previously noted, the heat transfer element is provided within a blood vessel of the body such that blood is cooled *in vivo* upon contact with the heat transfer element. The blood vessel can be arterial or venous. Where whole body hypothermia is desired, one preferred location for the heat transfer element is the inferior vena cava as discussed above.

To intravascularly regulate the temperature of a selected region, the heat transfer element may also be placed in a feeding artery of the region to absorb heat from the blood flowing into the region. For example, it is frequently desirable to provide neural protection within the brain under ischemic neural conditions. As previously noted, to selectively cool the brain, the heat transfer element can be placed, for example, into the common carotid artery, or both the common carotid artery and the internal carotid artery. The internal diameter of the common carotid artery ranges from 6 to 8 mm and the length ranges from 80 to 120 mm. Thus, the heat transfer element residing in one of these arteries should not be much larger than 4 mm in diameter in order to avoid occluding the vessel, which would actually act to exacerbate any ischemic neural damage.

A preferred method by which the heat transfer element is provided in either the inferior vena cava or the internal carotid artery is via entry at the femoral vein. The use of a heat transfer element to cool the body via the inferior vena cava is discussed above in connection with Figure 1. A schematic representation of the use of a heat transfer element in cooling the brain of the patient is shown in Figure 5. As in Figure 1, the apparatus of Figure 5 includes a working fluid supply 10, a supply catheter 12 and a heat transfer element 14. The principle of operation of the

apparatus of Figure 5 is similar to Figure 1, except that the heat transfer element 14 is positioned in the interior carotid artery.

In order to obtain neural protection under ischemic neural conditions, it is desirable to reduce the temperature of the blood flowing within the body or a portion of the body, such as the brain, to less than 35°C, more preferably between 30 and 35°C, and most preferably 32±2°C. In the case of the brain, given that a typical brain has a blood flow rate through each carotid artery (right and left) of approximately 250-375 cc/minute, the heat transfer element preferably absorbs 75-175 Watts of heat when placed in one of the carotid arteries, in order to induce the desired cooling effect. Approximate cooling time is 15 to 30 minutes.

A specific non-limiting example of a procedure for cooling the brain follows:

1. The patient is initially assessed, resuscitated, and stabilized.

2. The procedure is carried out in an angiography suite or surgical suite equipped with fluoroscopy.

3. Because the catheter is placed into the common carotid artery, it is important to determine the presence of stenotic atheromatous lesions. A carotid duplex (doppler/ultrasound) scan can quickly and non-invasively make this determinations. The ideal location for placement of the catheter is in the left carotid so this may be scanned first. If disease is present, then the right carotid artery can be assessed. This test can be used to detect the presence of proximal common carotid lesions by observing the slope of the systolic upstroke and the shape of the pulsation. Although these lesions are rare, they could inhibit the placement of the catheter. Examination of the peak blood flow velocities in the internal carotid can determine the presence of internal carotid artery lesions. Although the catheter is placed proximally to such lesions, the catheter may exacerbate the compromised blood flow created by these lesions. Peak systolic velocities greater that 130 cm/sec and peak diastolic velocities >100 cm/sec in the internal carotid indicate the presence of at least 70% stenosis. Stenosis of 70% or more may warrant the placement of a stent to open up the internal artery diameter.

4. The ultrasound can also be used to determine the vessel diameter and the blood flow, and the catheter with the appropriately sized heat transfer element can be selected.

5. After assessment of the arteries, the patient's inguinal region is sterilely prepped and infiltrated with lidocaine.

6. The femoral artery is cannulated and a guide wire may be inserted to the desired carotid artery. Placement of the guide wire is confirmed with fluoroscopy.

7. An angiographic catheter can be fed over the wire and contrast media injected into the artery to further to assess the anatomy of the carotid.

8. Alternatively, the femoral artery is cannulated and a 10-12.5 french (f) introducer sheath is placed.

9. A guide catheter can be placed into the desired common carotid artery. If a guiding catheter is placed, it can be used to deliver contrast media directly to further assess carotid anatomy.

10. A 10 f-12 f (3.3- 4.0 mm) (approximate) cooling catheter is subsequently filled with saline and all air bubbles are removed.

11. The cooling catheter is placed into the carotid artery via the guiding catheter or over the guidewire. Placement is confirmed with fluoroscopy.

12. Alternatively, the cooling catheter tip is shaped (angled or curved approximately 45 degrees), and the cooling catheter shaft has sufficient pushability and torqueability to be placed in the carotid without the aid of a guide wire or guide catheter.

13. The cooling catheter is connected to a pump circuit, also filled with saline and free from air bubbles. The pump circuit has a heat exchange section that is immersed into a water bath and tubing that is connected to a peristaltic pump. The water bath is chilled to approximately 0° C.

14. Cooling is initiated by starting the pump mechanism. The saline within the cooling catheter is circulated at 5 cc/sec. The saline travels through the heat exchanger in the chilled water bath and is cooled to approximately 1° C.

15. It subsequently enters the cooling catheter where it is delivered to the heat transfer element. The saline is warmed to approximately 5- 7° C as it travels along

the inner lumen of the catheter shaft to the end of the heat transfer element.

16. The saline then flows back through the heat transfer element in contact with the inner metallic surface. The saline is further warmed in the heat transfer element to 12-15° C, and in the process, heat is absorbed from the blood, cooling the blood to 30° C to 32° C.

17. The chilled blood then goes on to chill the brain. It is estimated that 15-30 minutes will be required to cool the brain to 30 to 32° C.

18. The warmed saline travels back down the outer lumen of the catheter shaft and back to the chilled water bath where it is cooled to 1° C.

19. The pressure drops along the length of the circuit are estimated to be 2-3 atmospheres.

20. The cooling can be adjusted by increasing or decreasing the flow rate of the saline. Monitoring of the temperature drop of the saline along the heat transfer element will allow the flow to be adjusted to maintain the desired cooling effect.

21. The catheter is left in place to provide cooling for 12 to 24 hours.

22. If desired, warm saline can be circulated to promote warming of the brain at the end of the therapeutic cooling period.

In each of the various embodiments of the present invention, once the medical procedure is completed, the heat transfer element is preferably used to warm the body back to its normal temperature, i.e., 37 °C.

Regarding the construction of the heat transfer element, this component is ideally a flexible element, allowing it to be placed at the desired vascular position. For example, the element often has to be passed though a series of one or more venous or arterial branches, making flexibility an important characteristic of the heat transfer element.

Further, the heat transfer element is ideally constructed from a highly thermally conductive material such as metal or very thin plastics or polymers, in order to facilitate heat transfer. The use of a highly thermally conductive material increases the heat transfer rate for a given temperature differential between the fluid within the heat transfer element and the blood. Highly thermally conductive

materials, such as metals, tend to be rigid. Therefore, the design of the heat transfer element should facilitate flexibility in an inherently inflexible material.

In general, the magnitude of the heat transfer rate is proportional to the surface area of the heat transfer element, the temperature differential, and the heat transfer coefficient of the heat transfer element.

Diameter, and hence surface area, of the heat transfer element is limited to avoid significant obstruction of the vein or artery and to allow the heat transfer element to easily pass through the vascular system. As noted above, for placement within the inferior vena cava, the cross sectional diameter of the heat transfer element is about 4-5 mm. For placement in the internal carotid artery, the cross sectional diameter is about 2 to 3.5 mm. Typically, the length of the heat transfer element for this purpose is about 10 to 30 cm.

When used in cooling mode, decreasing the surface temperature of the heat transfer element can increase the temperature differential. However, the minimum allowable surface temperature is limited by the characteristics of blood. Blood freezes at approximately 0°C. When the blood approaches freezing, ice emboli may form in the blood that may lodge downstream, causing serious ischemic injury. Furthermore, reducing the temperature of the blood also increases its viscosity, which results in a small decrease in the value of the convection heat transfer coefficient. In addition, increased viscosity of the blood may result in an increase in the pressure drop within the artery or vein, thus compromising the flow of blood to the organs. Given the above constraints, it is advantageous to limit the minimum allowable surface temperature of the heat transfer element to approximately 5° C. This results in a maximum temperature differential between the blood stream and the heat transfer element of approximately 32° C when the heat transfer device is used in cooling mode.

Similarly, when in heating mode, increasing the surface temperature of the heat transfer element can increase the temperature differential. Analogous to cooling, however, the maximum allowable surface temperature is limited by the characteristics of blood. In particular, damage to blood components can occur at temperatures of about 45-48° C and above. Accordingly, it is advantageous to limit

the maximum allowable surface temperature of the heat transfer element to approximately 44° C. This results in a maximum temperature differential between the blood stream and the heat transfer element of approximately 7° C when the heat transfer device is used in heating mode.

The mechanisms by which the value of the convection heat transfer coefficient may be increased are complex. However, it is well known that the convection heat transfer coefficient increases with the level of turbulent kinetic energy in the fluid flow. Thus it is advantageous to have turbulent or mixing blood flow in contact with the heat transfer element.

Specifically, creating a turbulent boundary layer on the heat transfer element surface can increase the heat transfer rate. In the event that a smooth heat transfer element is used, turbulence normally occurs in a very thin boundary layer, producing only a small amount of turbulent kinetic energy and resulting in less than optimal heat transfer. Therefore, to induce increase turbulent kinetic energy (and thus to increase the heat transfer rate), a stirring mechanism that abruptly changes the direction of velocity vectors is preferably utilized. This can create high levels of turbulence intensity in the free stream (and not just the boundary layer), thereby sufficiently increasing the heat transfer rate. If the flow of blood is continuous (non-pulsatile) flow (such as encountered in venous flow), this turbulence or mixing intensity should be maintained at all times. In the event that blood flow is pulsatile flow (such as is encountered in arterial flow), the mixing intensity should be maintained over a majority of the pulsatile period (e.g., the cardiac cycle).

To create the desired level of mixing intensity in the blood free stream, in one preferred embodiment, the heat transfer element is provided with a modular design. This design creates helical blood flow and produces a high level of mixing in the free stream by periodically forcing abrupt changes in the direction of the helical blood flow. Figure 2 is a perspective view of such a mixing inducing heat transfer element within a blood vessel. Mixed flow is indicated at point 114, in the free stream area. The abrupt changes in flow direction are achieved through the use of a series of two or more heat transfer segments, each comprised of one or more helical ridges.

The use of periodic abrupt changes in the helical direction of the blood flow in order to induce strong free stream turbulence or mixing may be illustrated with reference to a common clothes washing machine. The rotor of a washing machine spins initially in one direction causing laminar flow. When the rotor abruptly reverses direction, significant turbulent kinetic energy is created within the entire washbasin as the changing currents cause random turbulent motion within the clothes-water slurry.

Figure 3 is an elevation view of one embodiment of a heat transfer element 14. The heat transfer element 14 is comprised of a series of elongated, articulated segments or modules 20, 22, 24. Three such segments are shown in this embodiment, but one or more such segments could be used without departing from the spirit of the invention. As seen in Figure 3, a first elongated heat transfer segment 20 is located at the proximal end of the heat transfer element 14. A mixing-inducing exterior surface of the segment 20 comprises four parallel helical ridges 38 with four parallel helical grooves 26 therebetween. One, two, three, or more parallel helical ridges 38 could also be used. In this embodiment, the helical ridges 38 and the helical grooves 26 of the heat transfer segment 20 have a left hand twist, referred to herein as a counter-clockwise spiral or helical rotation, as they proceed toward the distal end of the heat transfer segment 20.

The first heat transfer segment 20 is coupled to a second elongated heat transfer segment 22 by a first bellows section 25, which provides flexibility and compressibility. The second heat transfer segment 22 comprises one or more helical ridges 32 with one or more helical grooves 30 therebetween. The ridges 32 and grooves 30 have a right hand, or clockwise, twist as they proceed toward the distal end of the heat transfer segment 22. The second heat transfer segment 22 is coupled to a third elongated heat transfer segment 24 by a second bellows section 27. The third heat transfer segment 24 comprises one or more helical ridges 36 with one or more helical grooves 34 therebetween. The helical ridge 36 and the helical groove 34 have a left hand, or counter-clockwise, twist as they proceed toward the distal end of the heat transfer segment 24. Thus, successive heat transfer segments 20, 22, 24 of the heat transfer element 14 alternate between having

clockwise and counterclockwise helical twists. The actual left or right hand twist of any particular segment is immaterial, as long as adjacent segments have opposite helical twist.

In addition, the rounded contours of the ridges 38, 32, 36 also allow the heat transfer element 14 to maintain a relatively atraumatic profile, thereby minimizing the possibility of damage to the blood vessel wall.

The bellows sections 25,27 are formed from seamless and nonporous materials, typically metals such as nickel, copper, etc. The structure of the bellows sections 25, 27 allows them to bend, extend and compress, which increases the flexibility of the heat transfer element 14 so that it is more readily able to navigate through blood vessels. The bellows sections 25, 27 also provide for axial compression of the heat transfer element 14, which can limit the trauma when the distal end of the heat transfer element 14 abuts a blood vessel wall. The bellows sections 25, 27 are also able to tolerate cryogenic temperatures without a loss of performance.

It may be desirable to treat the surfaces of the heat transfer element 14 to avoid clot formation. In particular, one may wish to treat the bellows sections 25, 27 because stagnation of the blood flow may occur in the convolutions, thus allowing clots to form and cling to the surface to form a thrombus. One means by which to prevent thrombus formation is to bind an antithrombogenic agent to the surface of the heat transfer element 14. For example, heparin is known to inhibit clot formation and is also known to be useful as a biocoating. Alternatively, the surfaces of the heat transfer element 14 may be bombarded with ions such as nitrogen. Bombardment with nitrogen can harden and smooth the surface and thus prevent adherence of clotting factors to the surface.

Figure 4 is a longitudinal sectional view of the heat transfer element 14 of an embodiment of the invention, taken along line 5-5 in Figure 3. Some interior contours are omitted for purposes of clarity. An inner tube 42 creates an inner coaxial lumen 42 and an outer coaxial lumen 46 within the heat transfer element 14. Once the heat transfer element 14 is in place in the blood vessel, a working fluid such as saline or other aqueous solution may be circulated through the heat transfer

element 14. Fluid flows up a supply catheter into the inner coaxial lumen 40. At the distal end of the heat transfer element 14, the working fluid exits the inner coaxial lumen 40 and enters the outer lumen 46. As the working fluid flows through the outer lumen 46, heat is transferred from the working fluid to the exterior surface 37 of the heat transfer element 14, or vice versa. Because the heat transfer element 14 is constructed from a high conductivity material, the temperature of its exterior surface 37 may reach very close to the temperature of the working fluid. The tube 42 may be formed as an insulating divider to thermally separate the inner lumen 40 from the outer lumen 46. For example, insulation may be achieved by creating longitudinal air channels in the wall of the insulating tube 42. Alternatively, the insulating tube 42 may be constructed of a non-thermally conductive material like polytetrafluoroethylene or some other polymer.

The same mechanisms that govern the heat transfer rate between the exterior surface 37 of the heat transfer element 14 and the blood also govern the heat transfer rate between the working fluid and the interior surface 38 of the heat transfer element 14. The heat transfer characteristics of the interior surface 38 are particularly important when using water, saline or other fluid that remains a liquid as the coolant. Other coolants such as Freon undergo nucleate boiling and create turbulence through a different mechanism. Saline is a safe coolant because it is non-toxic, and leakage of saline does not result in a gas embolism, which could occur with the use of boiling refrigerants. Since turbulence or mixing in the coolant is enhanced by the shape of the interior surface 38 of the heat transfer element 14, the coolant can be delivered to the heat transfer element 14 at a warmer temperature and still achieve the necessary heat transfer rate.

Further details and embodiments concerning the heat transfer element design and operation can be found in commonly assigned WO 99/48449, the complete disclosure of which is incorporated by reference.

Although the present invention has been described with respect to several exemplary embodiments, there are many other variations of the above-described embodiments that will be apparent to those skilled in the art. It is understood that

these variations are within the teaching of the present invention, which is to be limited only by the claims appended hereto.

What is claimed is:

1. A method comprising:

inducing hypothermia in a human patient in need of neural protection due to ischemic neural conditions, said step of inducing hypothermia comprising (a) positioning a heat transfer element in a blood vessel of a patient and (b) cooling the body of the patient or a region of the body of the patient to less than 35°C using said heat transfer element; and

administering to said patient a therapeutic agent selected from (a) a free-radical scavenger, (b) an N-methyl-D-aspartame receptor antagonist and (c) an antipyretic agent, said therapeutic agent being provided in an amount effective to supplement neural protection provided by said step of inducing hypothermia.

2. The method of claim 1, wherein said therapeutic agent is said antipyretic agent.

3. The method of claim 2, wherein said antipyretic agent has anti-inflammatory properties as well as antipyretic properties.

4. The method of claim 2, wherein said antipyretic therapeutic agent is dipyrone.

5. The method of claim 2, wherein said antipyretic agent is administered for at least three days after hypothermia is suspended.

6. The method of claim 1, wherein said therapeutic agent is said free radical scavenger.

7. The method of claim 6, wherein said free radical scavenger is selected from tirilazad and a salt thereof.

8. The method of claim 1, wherein said therapeutic agent is said N-methyl-D-aspartame receptor antagonist.

9. The method of claim 8, wherein said N-methyl-D-aspartame receptor antagonist is selected from the group consisting of dextromethorphan and a salt thereof.

10. The method of claim 1, wherein both said free radical scavenger and said N-methyl-D-aspartame receptor antagonist are administered to said patient.

11. The method of claim 10, wherein said free radical scavenger is selected from tirilazad and salts thereof and wherein said N-methyl-D-aspartame receptor antagonist is selected from dextromethorphan and salts thereof.

12. The method of claim 1, wherein said hypothermia is induced and said therapeutic agent is administered after said patient has experienced said ischemic neural conditions.

13. The method of claim 12, wherein said patient has experienced cerebral ischemia.

14. The method of claim 12, wherein said patient has experienced a stroke.

15. The method of claim 12, wherein said patient has experienced ischemia of the spinal cord.

16. The method of claim 12, wherein said hypothermia is induced within 6 to 12 hours after said patient has experienced said ischemic neural conditions.

17. The method of claim 1, wherein said hypothermia is induced and said therapeutic agent is administered before said patient experiences said ischemic neural conditions.

18. The method of claim 17, wherein said ischemic neural conditions arise in connection with brain surgery.

19. The method of claim 1, wherein the body of the patient or the region of the body of the patient is cooled to 30 to 35 °C.

20. The method of claim 1, wherein the body of the patient is cooled.

21. The method of claim 1, wherein the brain of the patient is cooled.

22. The method of claim 1, wherein the heat transfer element absorbs at least 75 Watts of heat during cooling.

23. The method of claim 1, further comprising warming the body of the patient or the region of the body of the patient to about 37 °C using said heat transfer element, subsequent to the step of inducing hypothermia.

24. The method of claim 1, wherein the heat transfer element is positioned in the venous vasculature.

25. The method of claim 1, wherein the heat transfer element is positioned in the arterial vasculature.

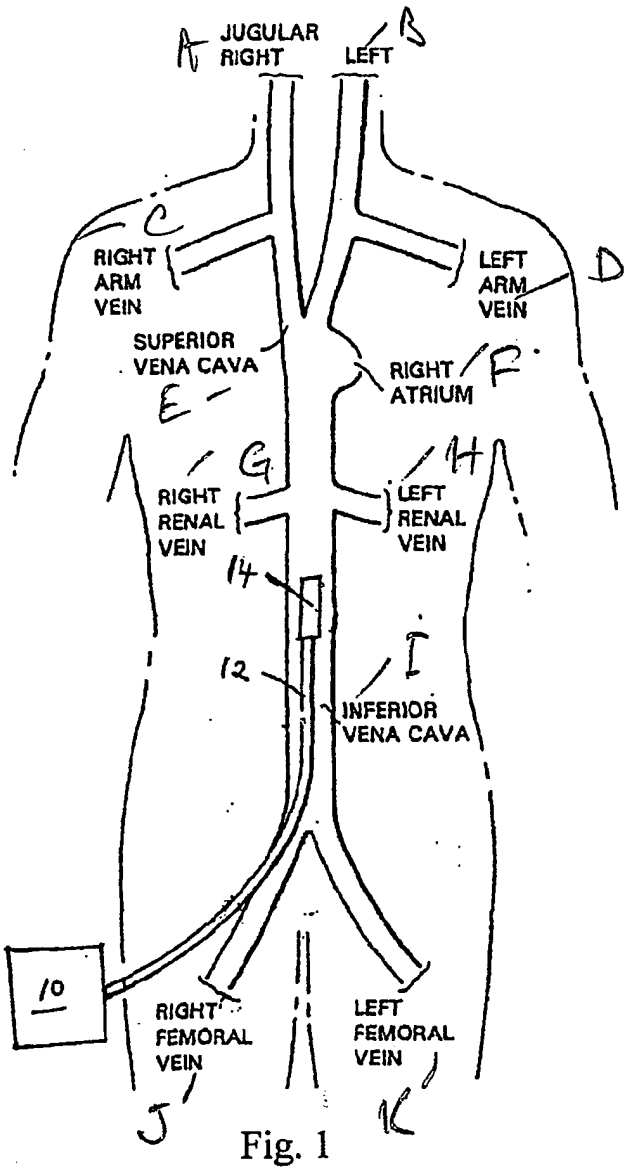
26. The method of claim 25, wherein the heat transfer element is positioned in the common carotid artery, the internal carotid artery, or concurrently in both the common carotid artery and the internal carotid artery.

27. The method of claim 1, wherein said heat transfer element is attached to a distal end of a flexible catheter, wherein said catheter is used in the step of positioning said heat transfer element in said blood vessel, and wherein said catheter is used to convey chilled fluid to the interior of said heat transfer element.

28. The method of claim 27, wherein the heat transfer element further comprises a plurality of exterior surface irregularities, said surface irregularities being shaped and arranged to create mixing in the blood.

29. The method of claim 28, wherein the heat transfer element further comprises a plurality of interior surface irregularities within said heat transfer element, said interior surface irregularities being shaped and arranged to create mixing in fluid within said heat transfer element.

30. The method of claim 29, wherein said interior and exterior surface irregularities comprise one or more helical ridges and one or more helical grooves.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C
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VEIN
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ATRIUM
F
G
RIGHT
RENAL
VEIN
H
LEFT
RENAL
VEIN
14
12
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Fig. 1

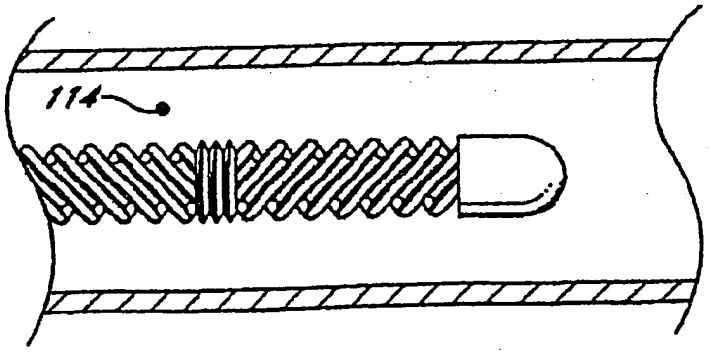
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Fig. 2

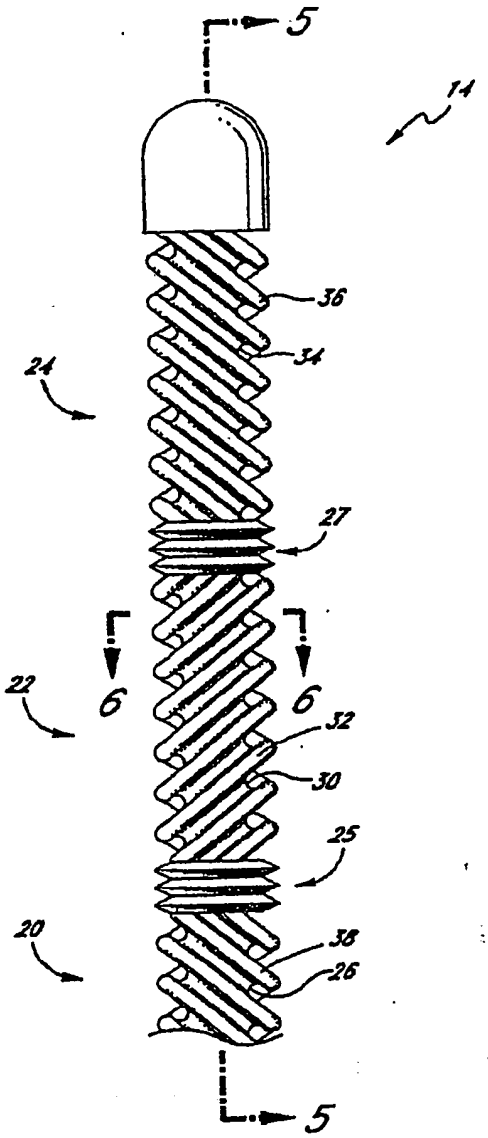

Fig. 3

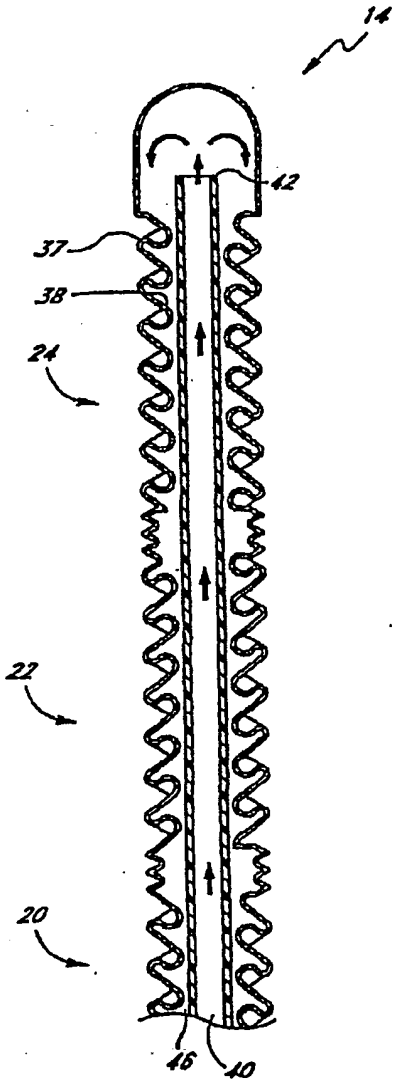

Fig. 4

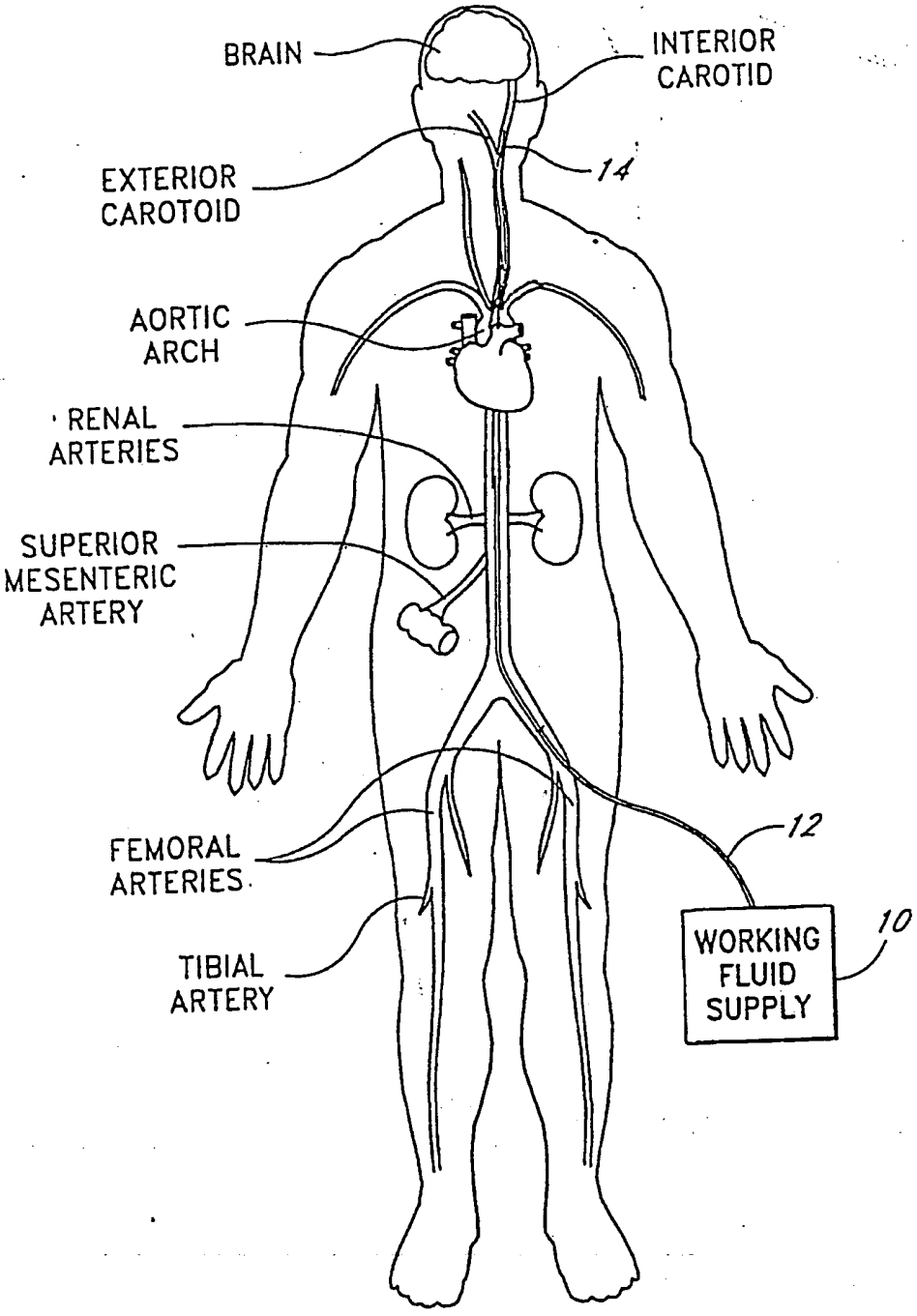
BRAIN
INTERIOR CAROTID
EXTERIOR CAROTOID
14
AORTIC ARCH
RENAL ARTERIES
SUPERIOR MESENTERIC ARTERY
FEMORAL ARTERIES
12
TIBIAL ARTERY
WORKING FLUID SUPPLY
10

FIG. 5